Public Workshop on Unapproved Drugs Preclinical Safety Requirements

January 9, 2007

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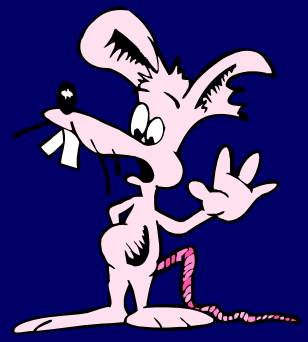
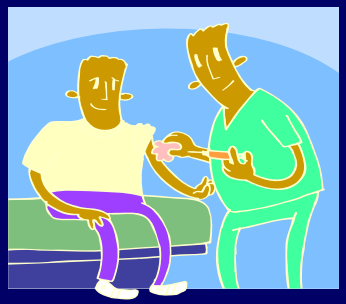
Examples of preclinical and nonclinical studies requested for an NME

- **Pharmacology (mechanistic and animal models, done in discovery, nonGLP)**
- **Safety pharmacology**
- **General toxicology**
- **Genetic toxicology**
- **Pharmacokinetics**
- **ADME (absorption, distribution, metabolism and excretion)**
- **Reproductive toxicology**
- **Carcinogenicity**
- **Special studies (e.g. juvenile)**



Why do we do ask for these studies?



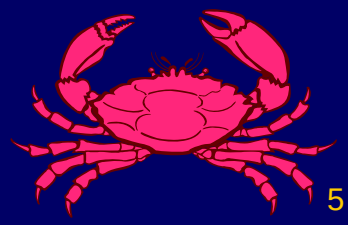
- **Determine whether it is safe to put drug candidate into humans**
- **Determine what constitutes an initial safe dose for human clinical trials**
- **Help determine a safe stopping dose**
- **Identify dose limiting toxicities (what should be monitored in clinical trials)**
- **Assess potential toxicities that cannot be identified in clinical trials**

Waivers for Toxicology Studies

- For unapproved drugs that have been widely marketed (time and extent) certain tests can be waived.
- Single and repeat dose toxicology studies designed to evaluate acute and chronic effects can be waived because of clinical experience. These include general toxicology and safety pharmacology studies.
- Some toxicities cannot be readily identified from clinical experience. The need for such studies will be evaluated on a case-by-case basis.

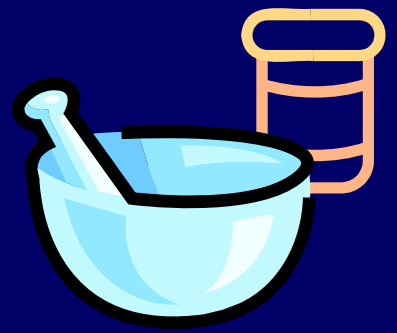
What toxicities cannot be easily identified by clinical experience?

- Genetic damage – not generally assessed.
- Effects on fertility – hard to detect.
- Teratogenicity - high background rate of birth defects, however potent teratogens should be detectable epidemiologically.
- Carcinogenicity - high background, long latency period makes epidemiological studies insensitive, especially for common cancers.
- Data that address these toxicities may be available in the open literature. The need for studies to address these potential toxicities will by on a case-by-case basis.



Factors considered in requirement for carcinogenicity studies.

- **Continuous use is for six months or more. Used frequently in an intermittent fashion for chronic or recurrent conditions (allergic rhinitis, anxiety, depression).**
- **Cause for concern:**
  - **Genotoxicity**
  - **Product class**
  - **Structure Activity Relationships (SAR)**
  - **Evidence from repeat-dose studies, e.g. hyperplasia**



What if carcinogenicity studies are positive: Issues to consider

- What is the drug indication?
- Who is the target population? Geriatric, pediatric, obstetric.
- What is the likely duration of use?
- Are there other drugs already serving this medical need? What is their safety profile?
- What is the margin of exposure (carcinogenic vs. clinical dose)?
- Usually a labeling issue.

Thank you for your attention. Questions?